(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 03/064531 A1

(51) International Patent Classification[7]: C08L 67/04, C08G 63/06, 63/78, D02J 1/22

(21) International Application Number: PCT/GB03/00400

(22) International Filing Date: 31 January 2003 (31.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0202233.3 31 January 2002 (31.01.2002) GB

(71) Applicant *(for all designated States except US)*: **SMITH & NEPHEW PLC** [GB/GB]; 15 Adam Street, London WC2N 6LA (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **ROSE, John** [GB/GB]; 62 Willow Park Road, Wilberfoss, York YO41 5PS (GB).

(74) Agent: **HOBBS, John**; Group Patents & Trade Marks Department, Smith & Nephew Group Research Centre, York Science Park, Heslington, York YO10 5DF (GB).

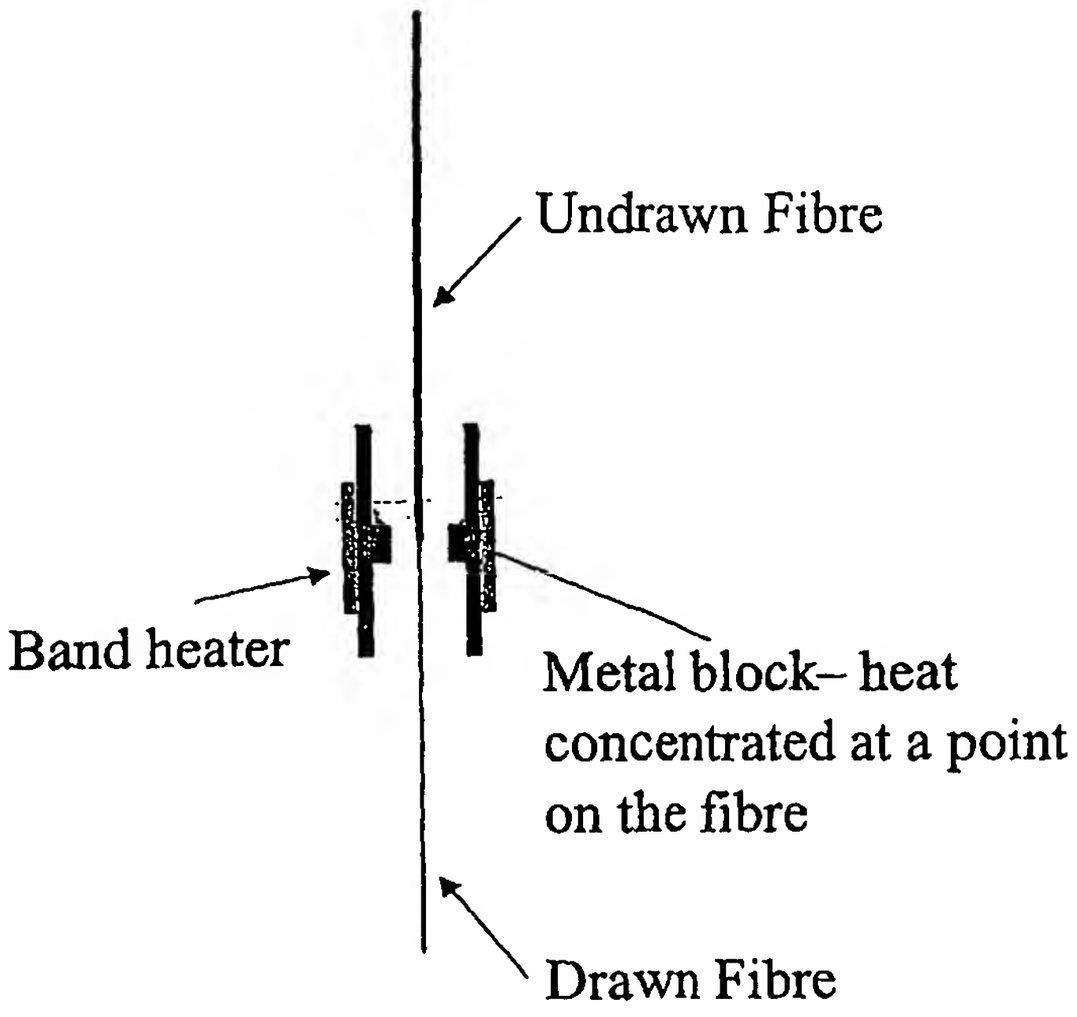
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: HIGH STRENGTH BIORESORBABLES CONTAINING POLY-GLYCOLIC ACID



(57) Abstract: Polymer compositions comprising poly-glycolic acid (PGA) or a functional derivative thereof with a tensile strength of at least 1200 MPa are disclosed. Processes suitable for manufacturing said compositions are also described, comprising rendering PGA into an amorphous state then drawing to form a highly orientated polymer structure. The polymer compositions can be used to make artefacts, for example sutures, or used in combination with other polymers or non-polymeric substances to produce other artefacts, for example medical devices suitable for implantation into the human body. Processes for the production of said artefacts are also described.

WO 03/064531 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

HIGH STRENGTH BIORESORBABLES CONTAINING POLY-GLYCOLIC ACID

The present invention relates to polymer compositions and artefacts made therefrom. In particular the present invention relates to polymers having high mechanical strength and their use for the manufacture of load bearing medical devices suitable for implantation within the body. More particularly the invention relates to bioresorbable poly-glycolic acid-containing polymers and to implantable medical devices made therefrom.

Polymer compositions comprising poly-glycolic acid (PGA) have an established use for medical implants. It has also been proposed that certain mechanical properties may be improved by extruding PGA melts or by drawing PGA in a plastic state. Isotropic PGA has a tensile strength of between 50 to 100 MPa and a tensile modulus of between 2 and 4 GPa. A commercial product (SR-PGA) comprising PGA fibres in a PGA matrix has a flex strength and modulus of 200 – 250 MPa and 12 – 15 GPa, respectively. It is also reported in the literature that melt spun PGAs have tensile strength of about 750 MPa and a modulus of from 15 to 20 GPa. In US Patent No. 4968317 an example of a drawn PGA is stated to have a tensile strength of about 600MPa.

Although PGAs having improved strength characteristics are known, none of the known materials have the mechanical properties approaching those of the metals conventionally used for load bearing implantable medical devices. A commercial alloy used for orthopaedic implant devices, known as Ti-6-4, comprises titanium with 6% aluminium and 4% vanadium and has a tensile strength in the range of 800 to 1000MPa and a modulus in the order of 100GPa.

One possible reason that PGA cannot currently be processed to achieve the desired strength of metals is that when PGA is processed by common methods to produce orientated fibres (e.g. stretching the material at a constant rate in a heated chamber or tank) additional crystallisation of the polymer occurs during the process. The crystals in the polymer act such that they prevent further orientation of the polymer. This crystallisation of the

polymer limits the mechanical properties that can be achieved by drawing PGA to around 800MPa, as described in the prior art.

We have found that polymer compositions comprising PGA may be processed such that the resultant composition has significantly greater strength, typically of the order of greater than 1200MPa with a commensurate increase in modulus, typically in excess of 22 GPa.

In accordance with the present invention there is provided a polymer composition comprising poly-glycolic acid or a functional derivative thereof having a tensile strength of at least 1200MPa.

The polymer composition gains this level of tensile strength by means of a novel processing method that results in an orientated structure, for example an orientated fibre.

The present invention further provides an artefact comprising a polymer composition including poly-glycolic acid or a functional derivative thereof having a tensile strength of at least 1200MPa.

The polymer composition may be comprised entirely of PGA or a derivative thereof, or may comprise a PGA-containing blend with other polymers. Preferably the polymer composition is entirely PGA.

Similarly, artefacts formed from the polymer compositions of the invention may consist wholly of the polymer compositions of the invention or may be composites consisting only partially of the polymer compositions of the invention.

Aptly the artefact contains 10 to 80% by volume of the polymer compositions of the invention, suitably the artefact contains up to 60% by volume of the polymer compositions of the invention, preferably the artefact contains at least 40% by volume of the polymer compositions of the invention and typically the artefact contains approximately 50% by volume of the polymer compositions of the invention.

We have found that in order to achieve the high strength exhibited by the compositions of the invention it is necessary that the PGA be rendered into an amorphous state and then immediately drawing to form a highly orientated structure.

This can be achieved by first processing isotropic PGA granules, which are commercially available, to form fibres or filaments, thereafter passing the fibres into a quenching bath to form an amorphous structure. Polymer compositions of the present invention may then be produced by drawing the quenched, amorphous PGA. Preferably this is a drawing process which minimises the time polymer is exposed to elevated temperatures, thus minimising the time for the polymer to crystallise.

In accordance with another aspect of the invention there is provided a process for the manufacture of poly-glycolic acid-based polymer compositions comprising increasing polymer chain orientation of a substantially amorphous polymer by drawing at localized points within the mass.

Suitably this comprises the steps of forming poly-glycolic acid or a functional derivative thereof into fibres, for example by melt extrusion or solution spinning; quenching the fibres then subjecting the quenched fibres to a tension under conditions whereby a defined region of the tensioned fibres is drawn.

Aptly fibres of amorphous PGA-containing polymers may be prepared by solution spinning or melt extruding the polymer through a die; the filament is then rapidly chilled to produce a substantially amorphous material. Typical chilling methods include blowing a cold gas onto the filament as it is produced or by passing the filament through a bath of a suitable cold liquid, e.g. water, silicone oil.

A suitable drawing method is zone heating. In this process a localised heater is moved along a length of fibre which is held under constant tension. This process is used in the zone-drawing process as described by Fakirov in

Oriented Polymer Materials, S Fakirov, published by Hüthig & Wepf Verlag, Hüthig GmbH. In order to carry out this zone heating fibre can be passed through a brass cylinder. A small part of the cylinder inner wall is closer to the fibre, this small region locally heats the fibre, compared to the rest of the brass cylinder, localising the drawing of the fibre to this location, see figure 1. A band heater can be placed around the brass cylinder to allow it to be heated above room temperature. This heated brass cylinder can then be attached to the moving cross-head of a tensile testing machine and the fibre to be drawn suspended from a beam attached to the top of the testing machine. To draw the fibre a weight can be attached to the lower end of the fibre, the brass cylinder heated to the desired temperature and the cross-head moved to the lower end of the fibre, see figure 2. The polymer draws where the fibre is closest to the brass cylinder, as the cross-head is moved up the length of the fibre, then a length of the fibre can be drawn.

Suitably the fibre can be held taut using a small stress, which is typically below the yield point of the material at ambient temperatures. The fibre can then be heated locally to a temperature which is above the softening point (T_g) but below the melting point such that localised drawing of the polymer occurs, the whole fibre can be treated by movement of either or both the fibre and heated zone such that the full length of the fibre is drawn. This first drawing of the polymer may produce a polymer with improved molecular alignment and therefore strength and modulus. In this first step the conditions are selected such that the material does not substantially crystallise during the process, this requires that either the temperature of the polymer is below the temperature at which crystallisation occurs, T_c, or if the polymer is above T_c the speed at which the heated zone moves along the fibres is fast enough such that the polymer cools below T_c before it has time to crystallise. Further improvements can be made by subsequent treatments, where the stress applied to the fibre or the zone temperature is increased or both. Both the strength of the fibre and the softening point increase as the degree of molecular alignment improves. The process can be repeated many times, until the desired properties are reached. A final annealing step can be carried out in which the material crystallises under tension in the process; this can further

improve the mechanical properties and improve the thermal stability of the final fibre.

In an embodiment of this aspect of the invention there is provided an artefact comprising a poly-glycolic acid in accordance with the invention. For example, the poly-glycolic acid fibres can be mixed with other components to form the artefacts. These other components may be polymers, bioresorbable polymers, non-polymeric materials or combinations thereof.

Aptly the bioresorbable polymer comprises a poly-hydroxy acid, a poly-caprolactone, a polyacetal, a poly-anhydride or mixture thereof; the polymer comprises poly-propylene, poly-ethylene, poly-methyl methacrylate, epoxy resin or mixtures thereof whilst the non-polymeric component comprises a ceramic, hydroxyapatite, tricalcium phosphate, a bioactive factor or combinations thereof.

Suitably the bioactive factor comprises a natural or engineered protein, a ribonucleic acid, a deoxyribonucleic acid, a growth factor, a cytokine, an angiogenic factor or an antibody.

Artefacts according to the present invention can aptly be manufactured by placing appropriate lengths of strengthened PGA fibre into moulds, adding the other components then compression moulding. Alternatively, the strengthened fibres can be pre-mixed with the other components then compression moulded.

In an alternative processing method, artefacts according to the present invention can be manufactured by forming a polymeric component in the presence of the strengthened fibres by in situ curing of monomers or other precursors for said polymeric component.

Preferably the monomers used in this process do not liberate any by-products on polymerisation as these can compromise the properties of the artefact.

Aptly at least one of the monomers used in said in situ curing process is a ring-opening monomer that opens to form a poly-hydroxy acid. Typically at

least one monomer is a lactide, a glycolide, a caprolactone, a carbonate or a mixture thereof.

The polymer compositions of the invention are useful for the production of medical devices, particularly implantable devices where it is desirable or necessary that the implant is resorbed by the body. Thus, artefacts in accordance with the present invention include sutures; tissue-engineering scaffolds or scaffolds for implantation; orthopaedic implants; reinforcing agents for long fibre composites used in resorbable load bearing orthopaedic implants; complex shaped devices, for example formed by injection moulding or extruding composites formed by mixing short lengths of chopped fibres with poly-lactic acid; or bone fixation devices, for example formed from relatively large diameter rods (e.g., greater than 1mm) of the compositions of the invention.

The invention will now be illustrated by the following examples.

Example 1

Isotropic PGA was extruded into a water bath to produce a translucent fibre of approx 0.5mm diameter. This fibre was then suspended vertically and a weight of 200g was applied. A heated cylinder of brass with a hole of approx 15mm apart from a small section with a 2mm diameter hole, through which the PGA fibre passes, was heated to a temperatures between 70°C and 100°C and moved along the fibre at a speed of 300 mm/min. The fibres were still translucent after this process, with the exception of the fibre processed with the bass cylinder set to a temperature of 100°C which was opaque. The resultant fibres were tested by mounting them at 22°C in a Zwick tensile testing machine, such that the length of fibre between the grips was 40mm. The sample was then pulled at a rate of 10mm/min. The resultant load - extension curve was recorded and the maximum load recorded was used to calculate the maximum strength of the fibre and the initial slope was used to calculate the modulus of the sample. The results are shown in figure 3.

Example 2

Isotropic PGA was extruded into a water bath to produce a translucent fibre of approx 0.5mm diameter. This fibre was then suspended vertically and a weight of 200g was applied. A heated cylinder of brass with a hole of approx 15mm apart from a small section with a 2mm diameter hole, through which the PGA fibre passes, was heated to a temperature of 90°C and moved along the fibre at a speed of 500 mm/min. The resultant fibre was still translucent after this process. The fibre produced was tested, as described below, and found to have a strength of 1780 MPa and a modulus of 26.7 GPa.

Example 3

PGA fibre was produced as in example 2, and then the drawn PGA fibre was re-drawn using a temperature of 90°C and a speed of 500mm/min for the zone, with a weight of 500g applied to the fibre. The fibre produced was opaque indicating that crystallization of the polymer had occurred in this process step. When tested the fibres were found to have a strength of 2400MPa and a modulus of 40.8 GPa.

Example 4

A block of PTFE was machined to form a two-part mould for a fixation plate, see figure 4. A reaction mixture was prepared by weighing 100g of DL-Lactide into a glass vial in a dry nitrogen atmosphere and sealed with a septum. 10 µl of a solution of $SnCl_2.2H_2O$ (1.00 g) in Di(ethylene glycol) (2.91g) were then injected into the monomer vial using a 25µl syringe. The vial was then heated in an oven at 150°C, once the monomer had completely melted; the vial was shaken to mix the contents. Braided fibres of drawn PGA, as made in Example 2, were first packed into the mould cavity (corresponding to 45% of the mould volume) and then the mould was placed in an oven at 150°C. Once the mould at reached temperature, the molten reaction mixture and mould were placed in a dry nitrogen atmosphere and the reaction mixture poured into the mould before either had cooled sufficiently for the monomer to crystallise. The filled mould was sealed then returned to the 150°C oven, vented by piercing the cap with a syringe needle. To remove air bubbles from

the fibre in the mould, the hot mould was transferred to a vacuum oven at 150°C. A vacuum of 1 mbar was applied, the oven was then re-pressurised with dry nitrogen; this was repeated once. The mould was then removed from the oven and the syringe needle vent removed. The mould was then placed in a conventional oven at 150°C for 6 days to cure the polymer.

After curing the mould was removed from the oven and allowed to cool to room temperature. The mould was then separated and the device removed from the mould. The DL-lactide had polymerized to form a translucent solid phase around the fibres.

Example 5

Using the same mould as for example 4 a fixation plate was made using L-lactide as the monomer precursor for the matrix. The catalyst, initiator and curing conditions were identical to those used in example 4. When the plate was removed from the mould it could be seen that the L-lactide had polymerized to form an opaque solid around the fibres.

Example 6

A block of PTFE was machined to form a two-part mould for a RCI screw, see figure 5. The catalyst, initiator and curing conditions used were identical to example 4 but the material used to form the matrix was a mixture of DL-lactide and glycolide in the ratio 85:15. Short fibres of drawn PGA (approx 2mm long), as made in example 2, were packed into the mould (corresponding to 30% of the mould volume). Once curing was complete the mould was left to cool and the device removed. The monomers had cured to form a solid translucent phase around the fibres.

CLAIMS

1. A polymer composition comprising poly-glycolic acid or a functional derivative thereof with a tensile strength of at least 1200MPa

2. A polymer composition of claim 1 formed into orientated fibres

3. A polymer composition of claims 1 to 2 where the fibres have a tensile modulus of at least 22GPa

4. A process for the manufacture of polymer compositions as claimed in claims 1 to 3 comprising increasing polymer chain orientation of a substantially amorphous polymer by drawing at localized points within the mass

5. A process for the manufacture of polymer compositions as claimed in any one of the preceding claims including the steps of forming poly-glycolic acid or a functional derivative thereof into fibres, quenching the fibres then subjecting the quenched fibres to a tension under conditions whereby a defined region of the tensioned fibres is drawn

6. A process according to claim 5 there the fibre-forming method is melt extrusion or solution spinning

7. A process according to claims 5 or 6 wherein the quenched, tensioned fibres are subjected to zone-heating

8. A process according to claims 5 to 7 wherein the quenched, tensioned fibres are subjected to at least two separate drawing steps, each drawing step performed under identical or different conditions

9. An artefact comprising poly-glycolic acid or a functional derivative thereof according to claims 1 to 3 or when produced by the process according to any one of claims 4 to 8

10. An artefact as claimed in claim 9 comprising at least two polymer components

11. An artefact according to claim 10 comprising 10% to 80% by volume poly-glycolic acid or a functional derivative thereof according to claims 1 to 3

12. An artefact of claims 10 or 11 wherein at least one of the polymer components is a co-polymer, or polymer blend

13. An artefact of claims 10 to 12 where at least one of the polymer components is bioresorbable

14. An artefact of claim 13 where the bioresorbable polymer comprises a poly-hydroxy acid, a poly-lactic acid, a poly-caprolactone, a poly-acetal or a poly-anhydride

15. An artefact of any of the preceding claims comprising at least one non-bioresorbable polymer component

16. An artefact of claim 15 where the non-bioresorbable polymer comprises poly-propylene, poly-ethylene, poly-methyl methacrylate or epoxy resin

17. An artefact of any of the preceding claims further containing at least one non-polymeric component

18. An artefact of claim 17 where the non-polymeric component comprises a ceramic, hydroxyapatite or tricalcium phosphate

19. An artefact of claims 17 or 18 where the non-polymeric component comprises a bioactive factor

20. An artefact of claim 19 where the bioactive component comprises a natural or engineered protein, a ribonucleic acid, a deoxyribonucleic acid, a growth factor, a cytokine, an angiogenic factor or an antibody

21. An artefact according to any of the preceding claims in the form of a medical device

22. An artefact of claim 21 where the device is a suture, a scaffold for tissue engineering or implantation, an orthopaedic implant, a complex shaped device or a bone fixation device

23. A process for the manufacture of artefacts according to claims 10 to 22 that further includes the step of compression moulding other polymeric, non-polymeric or blend of polymeric and non-polymeric components in the presence of said fibres

24. A process according to claims 10 to 23 further comprising forming a polymeric component in the presence of said fibres by in situ curing of monomers or other precursors for said polymeric component

25. A process according to claim 24 where the monomers used do not liberate a by-product on polymerization

26. A process according to claims 24 or 25 where at least one of the monomers is a ring-opening monomer that opens to form a poly-hydroxy acid

27. A process according to claims 24 to 26 where at least one monomer is a lactide, a glycolide, a caprolactone, a carbonate or mixtures thereof

28.

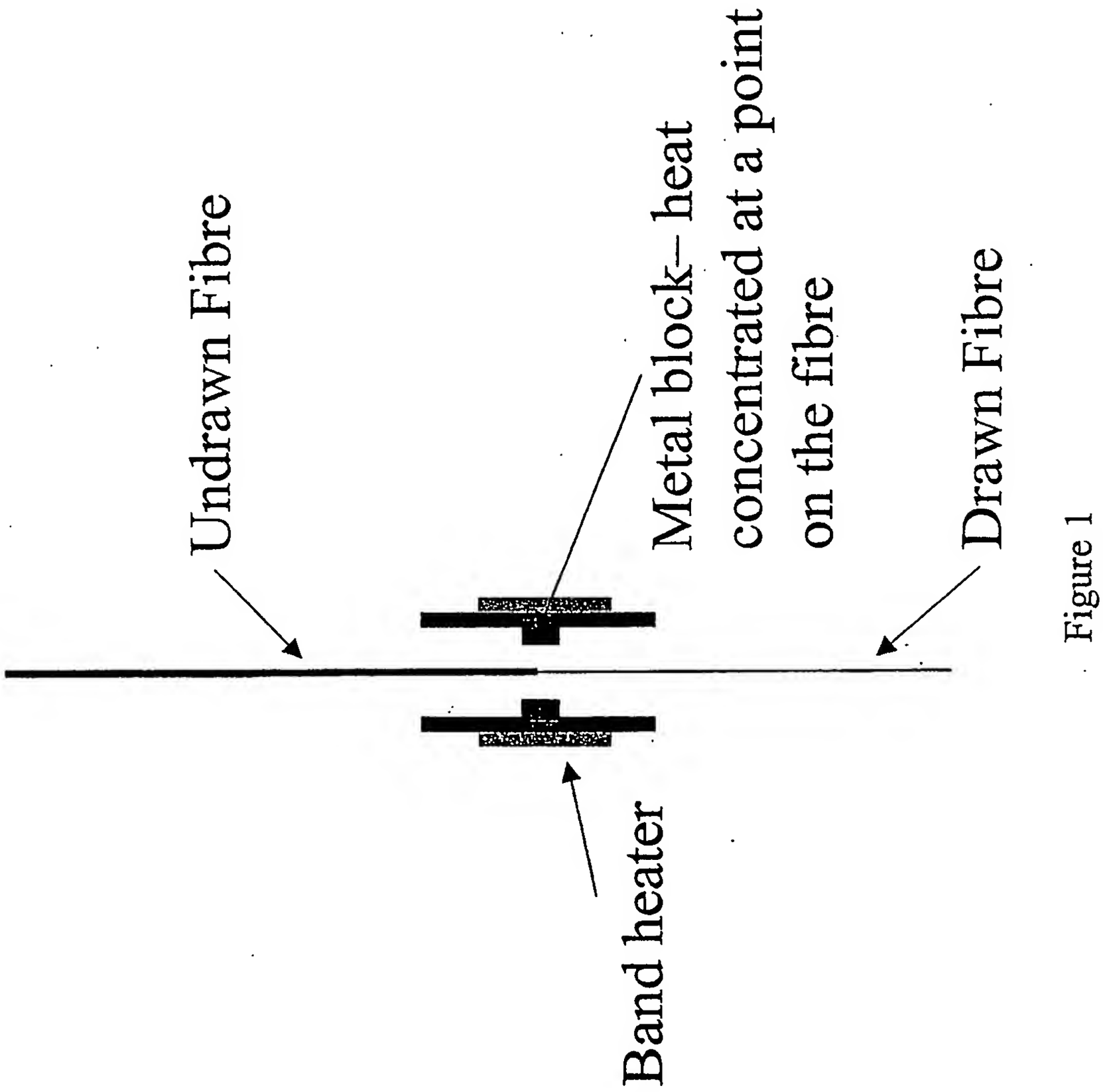

Undrawn Fibre
Metal block– heat concentrated at a point on the fibre
Drawn Fibre
Band heater

Figure 1

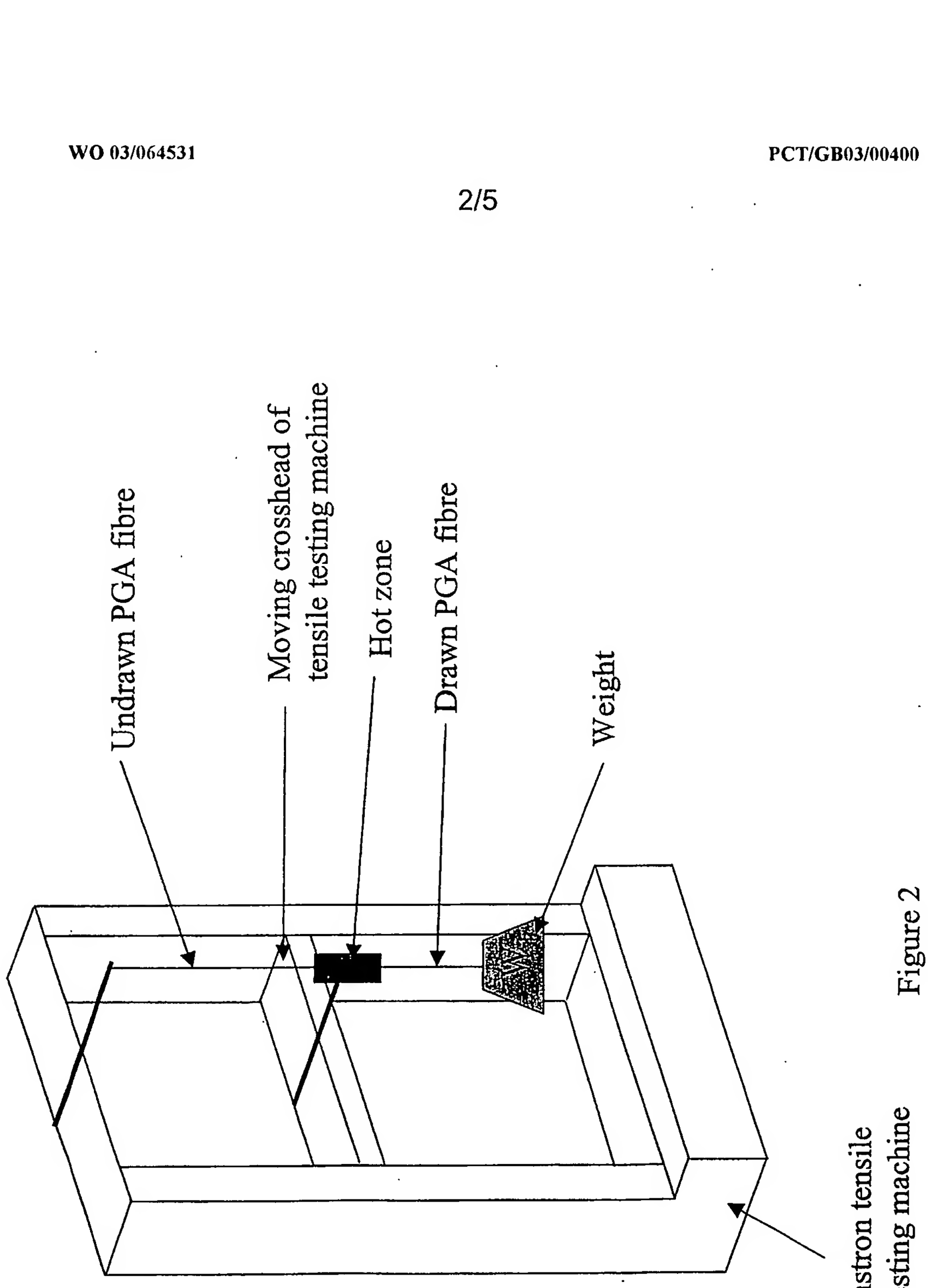

Undrawn PGA fibre
Moving crosshead of tensile testing machine
Hot zone
Drawn PGA fibre
Weight
Instron tensile testing machine

Figure 2

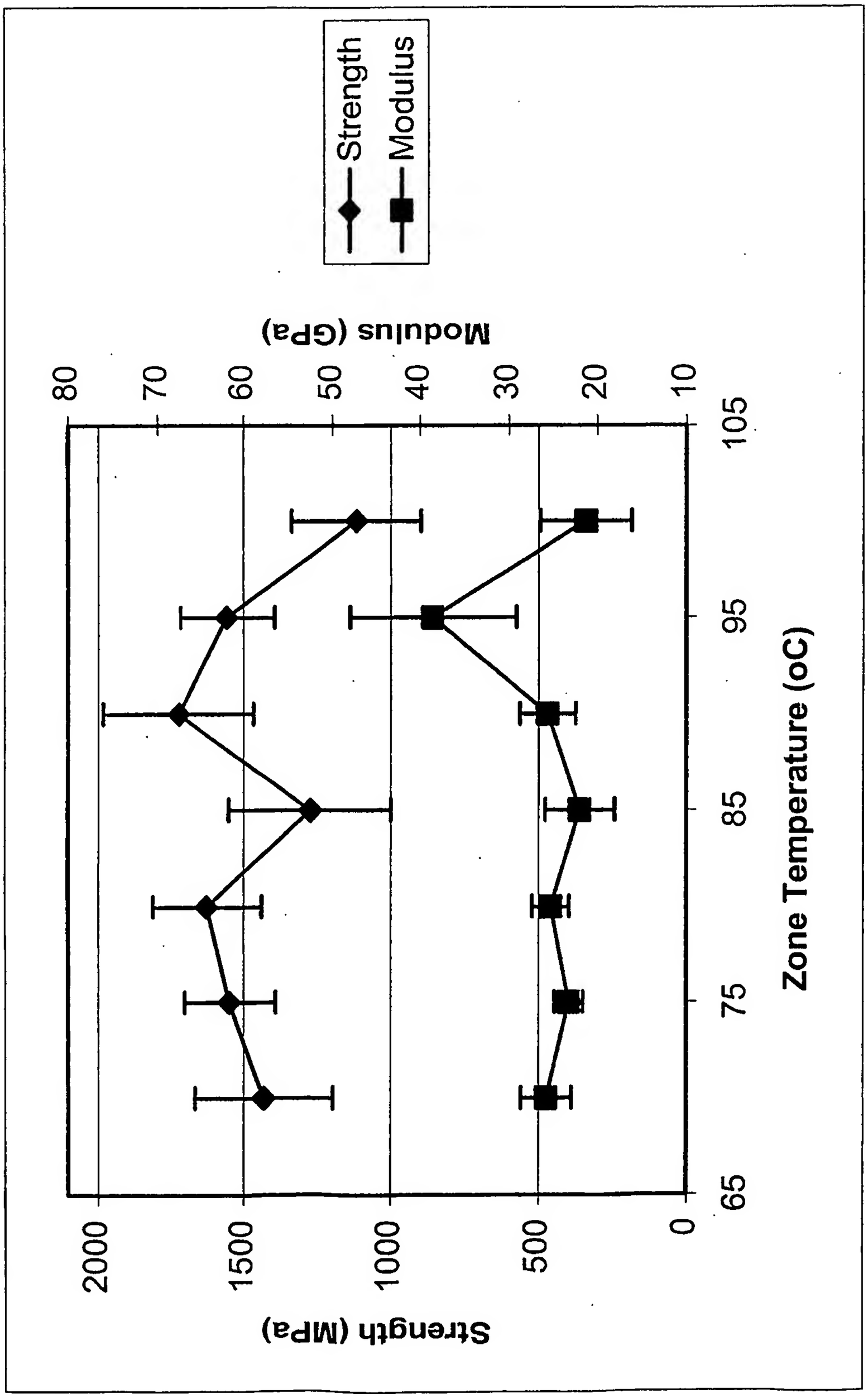

Strength
Modulus
Modulus (GPa)
80
70
60
50
40
30
20
10
105
95
85
75
65
Zone Temperature (oC)
2000
1500
1000
500
0
Strength (MPa)

Figure 3

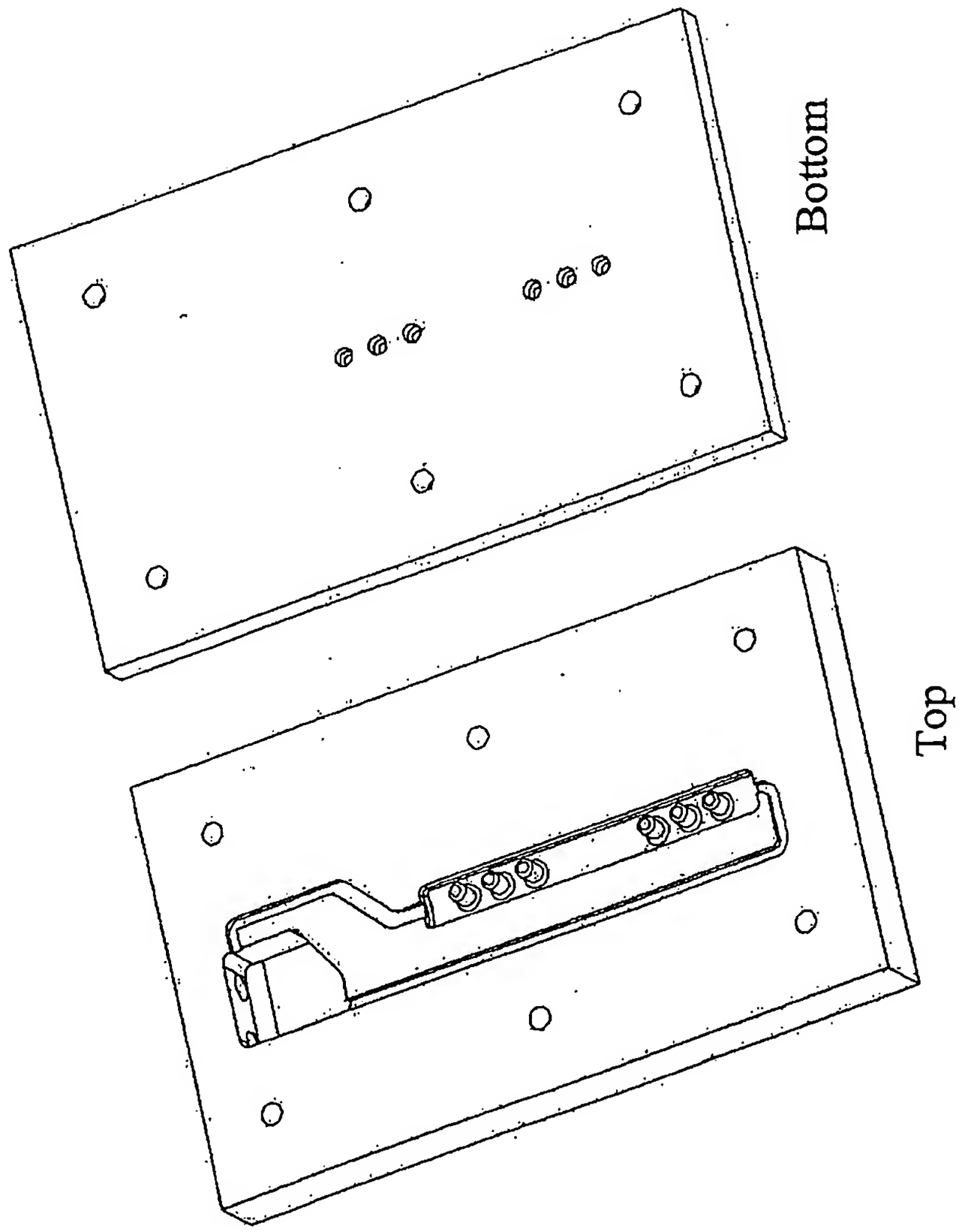


Figure 4

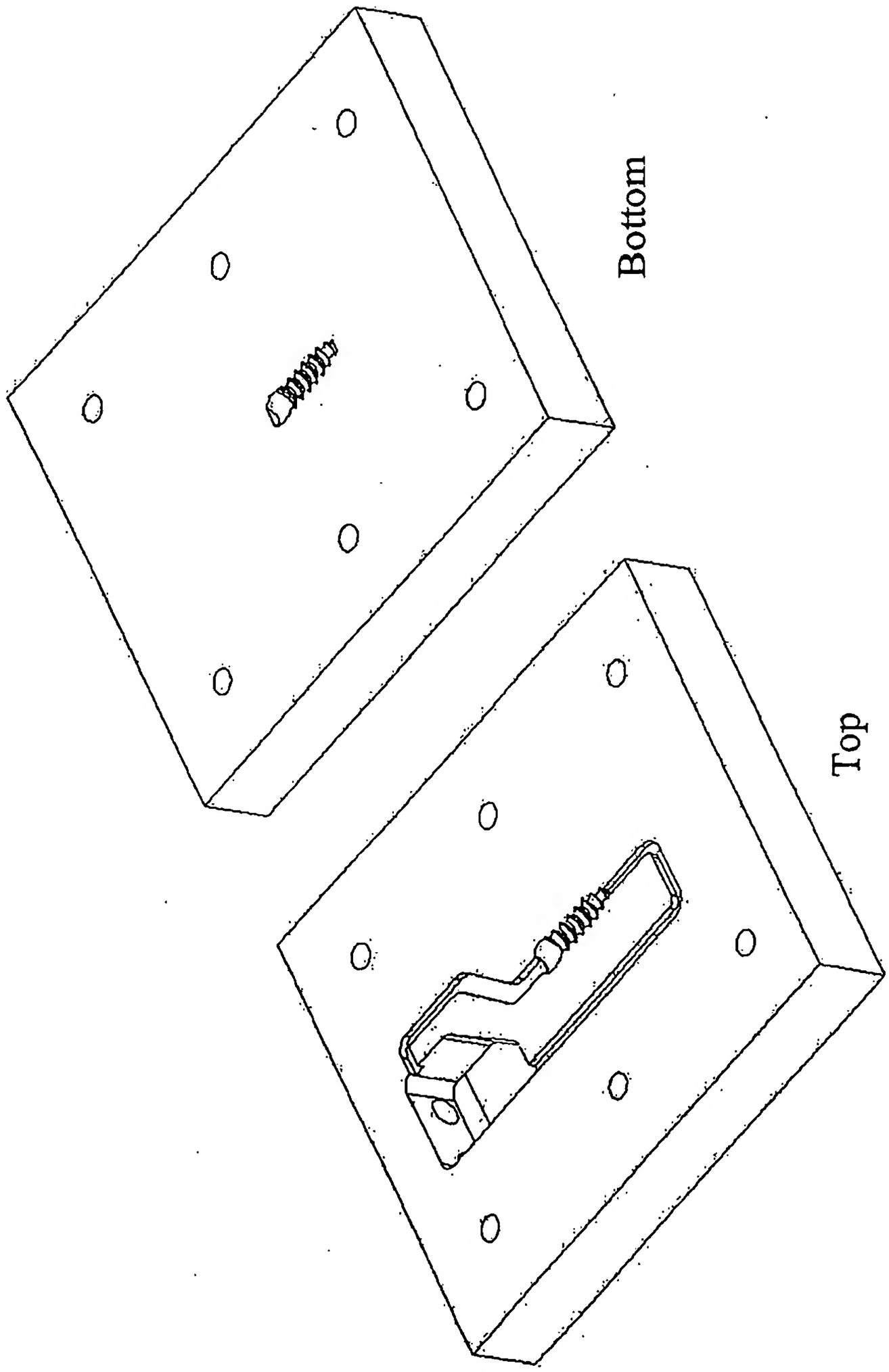


Figure 5

INTERNATIONAL SEARCH REPORT

Internatio pplication No
PCT/GB 03/00400

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08L67/04 C08G63/06 C08G63/78 D02J1/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08L C08G D02J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
COMPENDEX, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OKUZAKI HIDENORI ET AL: "Mechanical properties and structure of the zone-drawn poly(L-lactic acid) fibers" J POLYM SCI PART B;JOURNAL OF POLYMER SCIENCE, PART B: POLYMER PHYSICS 1999 JOHN WILEY & SONS INC, NEW YORK, NY, USA, vol. 37, no. 10, 1999, pages 991-996, XP001147427 page 991, column 2, paragraph 2 page 995, column 1, paragraph 1; table III ---	1-27
A	US 5 294 395 A (BROYER EPHRAIM) 15 March 1994 (1994-03-15) claim 1 column 4, paragraph 1 ---	9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2003	19/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauteschlaeger, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatio pplication No
PCT/GB 03/00400

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP 0 751 165 A (ETHICON INC) 2 January 1997 (1997-01-02) claim 1 page 6, line 45 - line 49 tables 1,2	1-27

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio pplication No
PCT/GB 03/00400

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5294395 A	15-03-1994	US 5451461 A	19-09-1995
		AU 625405 B2	09-07-1992
		AU 6198690 A	07-03-1991
		BR 9004338 A	03-09-1991
		CA 1337498 A1	07-11-1995
		DE 69027822 D1	22-08-1996
		DE 69027822 T2	02-01-1997
		EP 0415783 A2	06-03-1991
		ES 2088978 T3	01-10-1996
		GR 90100640 A ,B	20-01-1992
		IE 903173 A1	13-03-1991
		JP 3051433 B2	12-06-2000
		JP 3206143 A	09-09-1991
		PT 95162 A ,B	22-05-1991
		ZA 9006978 A	27-05-1992
EP 0751165 A	02-01-1997	US 5633343 A	27-05-1997
		AU 5608596 A	09-01-1997
		BR 9602945 A	28-04-1998
		CA 2180063 A1	31-12-1996
		EP 0751165 A2	02-01-1997
		JP 9012689 A	14-01-1997